DOSE-RESPONSE RELATIONSHIP FOR MYDRIASIS PRODUCED BY TOPICAL OCULAR TYRAMINE IN MAN

Tyramine is an indirectly acting sympathomimetic amine which is actively transported into sympathetic nerve terminals from which it causes the release of noradrenaline. Tyramine eyedrops thus cause dilatation of the pupil. The mydriatic response to tyramine is modified by drugs which act at the sympathetic neuro-effector junction, and this has provided a useful technique in the investigation of such drugs as tricyclic antidepressants (Ghose, 1976; Szabadi, Besson & Bradshaw, 1975) monoamine oxidase inhibitors (Bevan-Jones & Lind, 1971) and guanethidine (Sneddon & Turner, 1969).

In published studies, tyramine has generally been administered from a standard eye-dropper. Such droppers deliver a volume of 50–75 µl, much of which overflows from the conjunctival sac which holds a maximum of 30 µl (Chrai, Patton, Mehta & Robinson 1973). The administration of such large volumes ensures that the immediate concentration of drug in the tear film will closely approximate that of the instilled solution (Chrai, Makoid, Erikson & Robinson, 1974). However, this is not an acceptable way of delivering a known absolute dose of tyramine. Little attention has been paid to dose-response relationships for tyramine eyedrops, although in one study (Palm, Fengler, Gullner, Planz, Quiring, May, Helmstaedt, Lemmer, Moon & Holler, 1970) there was a clear difference in pupillary effect between 120 µg and 500 µg of tyramine. Reduction of the instilled volume facilitates accurate dosing and increases ocular bio-availability of a given dose of drug (Patton & Francoeur, 1977), thus enabling detailed investigation of the dose-response relationship.

Subjects for the present investigation were six healthy blue-eyed Caucasian male volunteers aged 27–37 years. A commercially available 2.5% solution of tyramine ('Mydrial', Winzer, Germany) was used undiluted as well as in 10 × and 100 × dilutions in water. Each volunteer was given a 5 µl and a 15 µl dose of each solution of tyramine. Thus, six doses were used: 1.25 µg, 4.75 µg 12.5 µg, 47.5 µg, 125 µg, and 475 µg. Subjects were dosed twice weekly with a minimum of 48 h between doses. The six doses were given in ascending order. In three subjects a seventh dose was given, this being a repetition of a dose (47.5 µg) from the middle of the dose range studied. Each dose was given onto the right conjunctiva using a 'Pipetman' P20 automatic micropipette with a sterilised disposable tip. On each study day the volunteer's eyes were photographed using a camera attached to a headframe which also carried twin flash lamps. Background illumination was constant artificial light. Photographs were taken before dosing, every 15 min for the first hour after dosing, every 30 min for 2 h

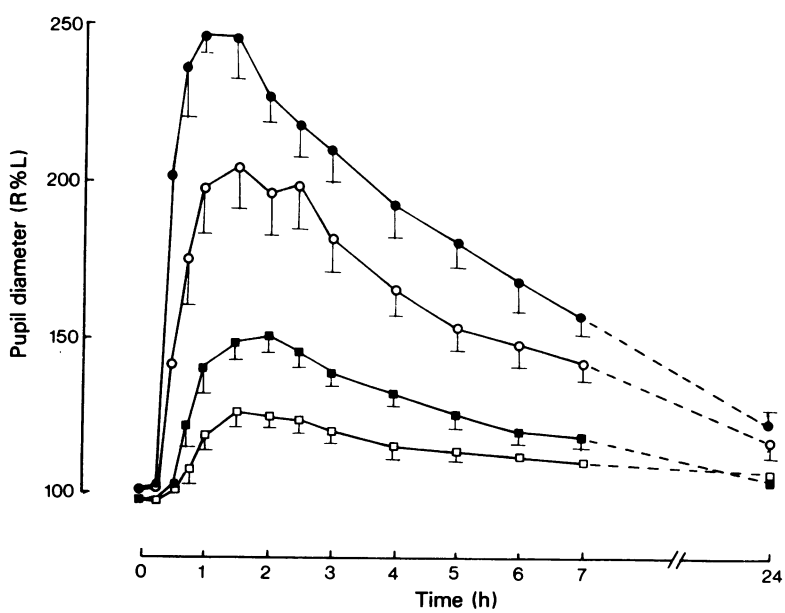

Figure 1 Time course of the mydriasis (mean ± s.e. mean) produced by four doses of topical ocular tyramine (□ 12.5 µg ■ 47.5 µg ○ 125 µg, ● 475 µg). The size of the right (treated) pupil is expressed as a percentage of the left (control) pupil. $n=6$ for each dose.

thereafter, hourly for 4 h after that and also at 24 h after dosing.

The photographic negatives were enlarged by projection onto a screen at a fixed distance, and pupillary diameters were measured with a ruler.

The two lowest doses did not produce mydriasis. The time-course of the mydriasis produced by the four higher doses is shown in Figure 1. The size of the treated (right) pupil has been expressed as a percentage of the untreated (left) control pupil at each time point. Both the peak effect and the duration of the effect are clearly dose-related. The mydriasis produced by the two highest doses was still obvious at 24 h after dosing. The log dose-response curve calculated from the peak response of each volunteer at each dose is shown in Figure 2.

Figure 3 shows data from the three subjects who were given a repeat dose of 47.5 μg tyramine. The effects of the second dose closely parallel those of the first. This indicates that observed effects are closely reproducible within individuals, as well as providing evidence that tachyphylaxis did not occur as a result of the rising dose schedule which was used.

When interaction with intraocular tyramine is to be used in the investigation of a drug acting at the sympathetic neuro-effector junction, then accurate administration of a predetermined dose of tyramine may be more sensitive than the standard method using an eye-dropper.

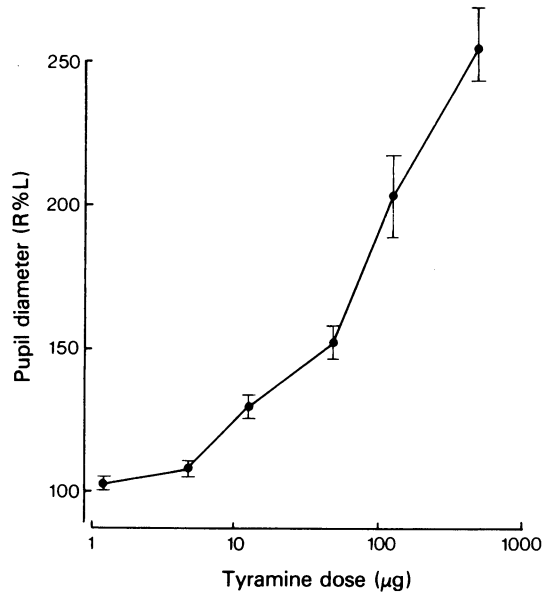

Figure 2 Dose-response curve for the maximal mydriatic effect (mean ± s.e. mean) of six doses of tyramine in six subjects. The size of the right (treated) pupil is expressed as a percentage of the left (control) pupil.

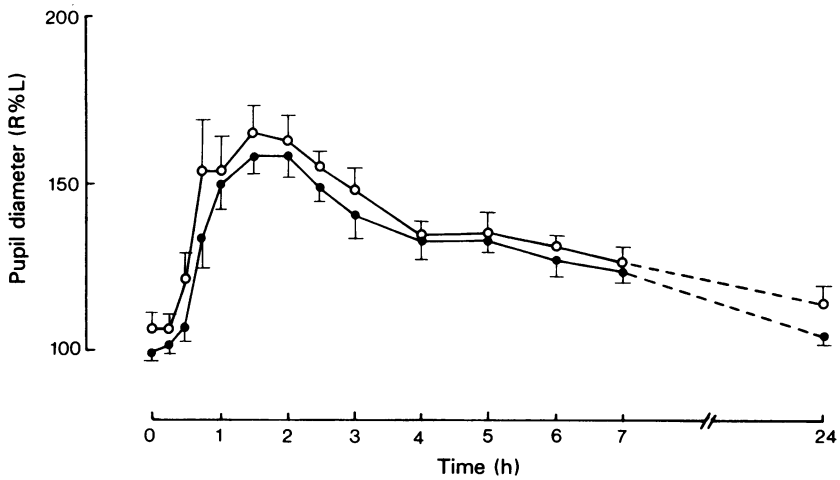

Figure 3 Time course of mydriasis (mean ± s.e. mean) produced by 47.5 μg tyramine given on two separate occasions to three subjects. The size of the right (treated) pupil is expressed as a percentage of the left (control) pupil. ● first dose, ○ second dose.

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DEPRENYL IS A SELECTIVE INHIBITOR OF BRAIN MAO-B IN THE LONG-TERM TREATMENT OF PARKINSON'S DISEASE

Deprenyl is a selective inhibitor of monoamine oxidase (MAO) type B (Knoll, 1976) that does not induce the hypertensive response to oral tyramine (Elsworth, Glover, Reynolds, Sandler, Lees, Phuapradit, Shaw, Stern & Kumar, 1978) (the 'cheese effect') which limits the use of other MAO inhibitors. It has been found to be of therapeutic benefit in Parkinson's disease when administered in conjunction with L-Dopa and a peripheral decarboxylase inhibitor (Birkmayer, Riederer, Youdim & Linauer, 1975; Birkmayer, Riederer, Ambrozi & Youdim, 1977; Lees, Shaw, Kohout, Stern, Elsworth, Sandler & Youdim, 1977). This effect is thought to be due, at least in part, to an increase in brain dopamine since MAO type B is reported to be responsible for the oxidation of this neurotransmitter in man (Glover, Sandler, Owen & Riley, 1977).

In vitro studies of deprenyl inhibition of human brain MAO show a concentration of 10^{-6} mol l^{-1} to be selective towards the B-form, while oxidation of 5-hydroxytryptamine, and MAO-A substrate, is hardly effected (Glover *et al.*, 1977). However, recent post mortem studies have shown that *in vivo* this selectivity is less pronounced (Riederer, Youdim, Rausch, Birkmayer, Jellinger & Seemann, 1978) (see Table 1), an equivalent concentration inhibiting 5-hydroxytryptamine oxidation by approximately 70%. Indeed, a Parkinsonian patient dying from the progression of the disease after 7 days treatment with 100 mg deprenyl daily (ten-fold the normal dose) exhibited total inhibition of all MAO activity with a consequent rise in the brain levels of dopamine and 5-hydroxytryptamine (Riederer *et al.*, 1978). Thus to understand the mechanism of action of deprenyl in

Table 1 Percentage inhibition (mean ± s.e. mean) of human brain MAO after deprenyl treatment

Substrates:	*Dopamine*		*5-hydroxytryptamine*	
Treatment:	*Short term*	*Long term*	*Short term*	*Long term*
Caudate	85.6 ± 1.8	89.0	65.7 ± 5.0	70.3
Putamen	83.4 ± 2.2	89.2	61.7 ± 5.7	66.1
Pallidum	86.5 ± 1.9	90.5	70.8 ± 3.7	74.4
Thalamus	86.0 ± 4.2	77.3	50.0 ± 6.8	55.7
S. nigra	88.0 ± 2.2	88.7	74.5 ± 4.0	66.7
Raphé	86.0 ± 2.6	85.4	70.6 ± 4.1	72.3
Amygdalae	82.0 ± 2.8	85.6	70.3 ± 4.5	69.8

Short term: seven patients treated with 10 mg deprenyl for 6 ± 1.8 days.
Long term: one patient treated with 10 mg deprenyl for over 4 years.